The mystery of sudden infant death syndrome

Hypotheses about why infants, suddenly stop breathing and die.

Hanna Marie Gustafsson

Department of forensic pathology and clinical forensic medicine
Institute of Public health
Faculty of medicine

University of Oslo

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Abstract:

Sudden infant death syndrome (SIDS) is defined as the sudden unexpected death of an infant < 1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history. Despite declines in incidence during the past two decades following the Back to Sleep campaigns, SIDS remains the leading cause of death for infants in developed countries. Epidemiological studies have identified modifiable risk factors such as prone and side sleep positions, smoke exposure, bed sharing, soft bedding and overheating. Pacifier use at sleep time is associated with decreased risk of SIDS. The cause of sudden infant death syndrome is unknown, but it is generally accepted that SIDS likely marks the end of a series of risk factors and pathophysiological responses. Given the complexity of the SIDS research, the following literature review represents only a brief overview of the epidemiology, pathology and pathogenesis of SIDS, focusing on brainstem abnormality, long QT-interval, infection and hypoxemia. Controversial issues regarding the classification and diagnosis are discussed.

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1 Introduction

Sudden infant death syndrome is a term used to describe unexpected death in infancy when subsequent investigations fail to demonstrate a definite cause of death. Such deaths have occurred for centuries, with the first reference being the judgment of Solomon in the Book of Kings in the Bible[1], where a woman was thought to have lost her infant due to "overlaying". Overlaying, the suffocation of an infant by a co-sleeping adult was considered to be responsible for the majority of unexpected infant deaths well into the twentieth century[1]. Researchers have investigated possible causes of SIDS and the factors associated with an increased or decreased risk of occurrence, but the underlying mechanisms are still poorly understood and effective preventive measures are still lacking.

The incidence of sudden infant death syndrome has declined the past two decades following the identification of several behavioral risk factors and their subsequent modification through public education campaigns. Nonetheless, SIDS remains the leading cause of death for infants aged between 1 month and 1 year in developed countries[2].

Sudden infant death syndrome research has been of varying quality and some theories are espoused with little supportive data[1]. Given the complexity of the SIDS research, the following literature review represents only a summary of selected theories and current issues. Controversial issues regarding the classification and diagnosis are discussed.

2 Methods

I searched the PubMed database to identify relevant articles. Included theories and issues were selected in consultation with adviser. I made following search (SIDS) AND (definition), (SIDS) AND (prone sleeping), (SIDS) AND (Smoking), (SIDS) AND (Bed-sharing), (SIDS) and (Overheating), (SIDS) AND (Pacifier), (SIDS) and (Serotonin), (SIDS) and (Long QT syndrome), (SIDS) and (Infection).

3 Definition

Sudden infant death syndrome is a term that has been used to describe unexpected death in infants or young children when subsequent investigations fail to demonstrate a definite cause of death[3]. The definition of SIDS has been up to debate since the first definition was proposed in 1965 and still today there is no generally definition.

The definition of sudden infant death syndrome originally appeared in 1969, at the Second International Conference on Causes of Sudden Death in Infants. It was proposed that SIDS was the sudden death of any infant or young child which is unexpected by history, and in which a thorough post mortem examination fails to demonstrate an adequate cause of death. The conference was initiated by parents and clinicians who recognized the need for consistent terminology in order to facilitate research and to reduce unwarranted suspicion of child abuse[3]. In 1994, the definition was modified and examination of the circumstances of death was included in the definition.[4]

In 2004, at the SIDS Redefinition Conference in San Diego, an expert panel developed a new general definition of SIDS for administrative and statistic purposes. This definition is stricter and more categorical, and was intended for use in research in order to enable more valid international comparisons. The definition includes a few positive diagnostic criteria, in comparison to previous definitions where SIDS is considered a diagnosis of exclusion.[5] The following definition with sub classification was agreed upon:

General Definition:

SIDS is defined as the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history.

Category I SIDS: so-called classic features must be present.

- Age between the third week and ninth month.
- Death occurring presumably during sleep.
- A normal clinical history including a full term pregnancy.

- No evidence of accidental death in the sleeping environment
- Complete absence of potential fatal pathological findings in autopsy.

Category II SIDS:

Includes the fully investigated infant deaths that do not meet the strict criteria in category I SIDS and cases where other possible death mechanisms are suspected, but not determined with certainty.

Unclassified Sudden Infant Death:

Includes infant deaths that do not meet the criteria for category I or II SIDS but for which alternative diagnosis of natural or unnatural conditions are equivocal, including cases for which autopsies were not performed.

4 Incidence

Norway experienced a dramatic increase in sudden infant death syndrome during the 1980s, concurrent with an increase in total post prenatal deaths[6]. Figure 1 shows the rate of SIDS in Norway from 1984 to 2005. During this period the incidence reached a peak with 142 cases of SIDS (2.4 ‰ of all live births) in 1988[7]. In 1990, recommendations to avoid putting infants to sleep in the prone position was given to the public in Norway, on the basis of preliminary reports from the Netherlands, England, New Zealand and Norway, which strongly suggested that prone sleeping was associated with SIDS[6]. These recommendations were followed by a sudden decline in the incidence of prone sleeping and sudden infant death syndrome, with 37 cases of SIDS in 1993 (0,6 ‰)[7]. The sudden decline in SIDS rates was a turning point and can probably be attributed to the decreased incidence of prone sleeping from 49% in 1989 to 27% in 1990.[8]

Norway had 15 cases of sudden infant death syndrome in 2011; two of the children were older than one year. Since 2001, the incidence rate has varied between 15 and 25 SIDS deaths per year. The rate seems to have reached a plateau, and sudden infant death syndrome is still one of the main causes of infant mortality in Norway today[7].

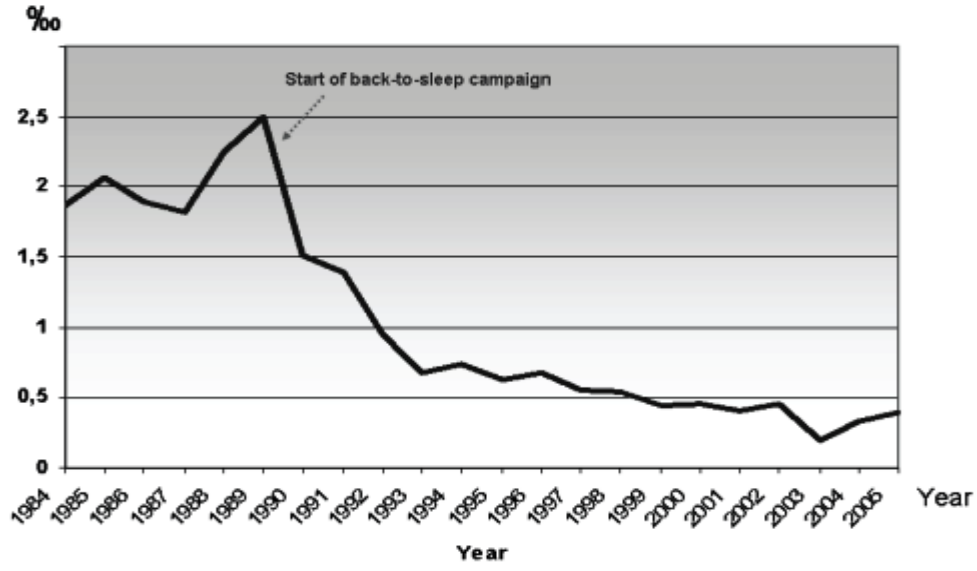

Figure 1. The SIDS rate (No of deaths pr 1000 live births) in Norway 1984-2005

Fig 1, Stray-pedersen et al 2008[71]

5 Epidemiology

5.1 Demographic factors

Boys are more likely to die from SIDS than girls at a ratio of 60:40[2]. Sudden infant death syndrome is associated with prematurity, low birth weight and low maternal age[9]. Infants are at greatest risk of SIDS at 2-4 months of age, with most SIDS-related deaths having occurred by 6 months[2]. This characteristic age peak has become less pronounced as the SIDS incidence has declined. Similarly, the commonly found seasonal variation, with most deaths occurring during the winter months from October to Mars, has declined as the infants sleeping in prone position have decreased. This claim supports a possible interaction between prone sleeping and factors more common during colder months as heavily wrapping and overheating[9].

The syndrome is seen in all social groups but is more prevalent in the socioeconomically deprived. The association between SIDS and socioeconomic factors has become more obvious since the decline in SIDS rate. Blair et al found a relative increased incidence of SIDS in deprived families from 47% to 74% [10].

Siblings of SIDS victims are at increased risk of dying of SIDS, which may be attributed to an unrecognized metabolic or genetic disorders and/or common environmental factors. Homicide should always be considered as a possibility, even if a sudden infant death in a subsequent sibling is six times more likely to be SIDS than homicide[2].

5.2 Sleep position

The prone sleeping position is the most significant independent risk factor for SIDS[11], with reported relative risks ranging from 3.5 to 9.6 for the last sleep. The side sleeping position has also been associated with an increased risk for SIDS, probably due to its instability making the infant vulnerable to fall over onto prone position[6].

The Nordic Epidemiological SIDS Study, a matched case-control study of 244 SIDS cases and 869 controls from 1992 to 1995 was conducted to investigate the combined effects of prone sleeping position and prenatal risk factors on the risk of SIDS. Parents of SIDS victims in Denmark, Norway, and Sweden completed a questionnaire on potential risk factor of SIDS.

The study reported that odds ratios for prone and side sleeping compared with supine sleeping for the last sleep were 13.9 and 3.5. Infants who were usually placed non-prone, but had been placed prone the last time, carried the highest risk[12].

Additional support for the association between prone sleeping position and increased risk of SIDS comes from various studies demonstrating the decreased rate of SIDS following the introduction of successful public health recommendations to place infants on their back to sleep[11].

Irgens et al performed a retrospective study to investigate the association between sleeping position of infants and the occurrence of SIDS. A questionnaire based surveillance of sleeping position was obtained in a random sample (n = 34 799) and surveillance of SIDS was based on all infants born in Norway 1967-91, surviving the prenatal period. The study managed to demonstrate a correlation between the epidemic of SIDS in Norway and the general view, in the 70s and 80s, that infants should be placed to sleep prone and that the dramatic drop in SIDS rate followed the Back to sleep campaign in 1990. The proportion of prone sleeping increased continuously from 7.4 % in 1970 to 49.1 % in 1989. Subsequently, the proportion dropped to 26.8 % in 1990. The SIDS proportion increased from 1.1/1000 to 2.6 in 1988 and 2.0 in 1989 and dropped to 1.1 in 1990[8].

While the proportion of prone sleeping infants has declined, the odds ratio for sudden infant death syndrome among prone sleepers has increased. In Norway, the odds ratio for infants sleeping prone was 2.0 before the back to sleep campaign and 11.0 after the campaign.[13] It has been argued that efforts intended to reduce further the prevalence of prone sleeping should target the populations groups that are at a particular risk for this prone sleeping practice[14].

5.2.1 Pathophysiological mechanisms of sleep position and SIDS

The mechanism for the increase in SIDS risk with the prone position is not known. Some studies have suggested that the prone position predispose to suffocation, triggered by decreased arousal, overheating and the type of bedding.

It has been reported that infants lying prone and face down in common bedding have an increased risk of rebreathing expired air, that contains a high level of CO2, resulting in hypercapnia and hypoxia[15]. Horne et al demonstrated that the prone position significantly

impairs arousal from both active and quiet sleep in healthy term infants at the age when SIDS incidence is highest[16]. It has been postulated that infants with blunted arousal systems may fail to turn their head or lift their face[17]. Thus, ventilatory or other life-threatening challenges, to which the normal responses might include arousal, may have more profound and potentially lethal effects in infants sleeping prone[16]. Wong et al demonstrated that placing infants to sleep in the prone position resulted in a decrease in cerebral oxygenation and suggested that this lowering may strengthen the reduced arousability of infants in the prone position[18].

Prone sleeping infants have a significantly reduced ability to lose heat, compared to supine sleeping infants, making them more susceptible to hyperthermia. It is believed that supine sleepers can lose more heat from the head compared to prone sleeping infants. They are also able to move more freely and can therefore expose limbs to increase heat loss and actively controlling their body temperature[19].

Ponsonby et al analyzed a case-control study of 58 infants with SIDS and 120 controls born and resident in Tasmania, Australia, attempting to identify effect modifiers of the relation between the prone sleeping position and SIDS. The researchers found that the association between sudden infant death syndrome and prone sleeping was significantly increased among infants who had a history of recent illness (P=0.02), but not among SIDS infant who slept in other positions. Prone sleeping infants may be at a particularly risk in connections with episodes of infection and fever. Fever puts an even greater demand on the body to get rid of heat[20].

5.3 Smoking

Since the reduction in the incidence of the prone sleeping position, maternal cigarette smoking has become the most important modifiable risk factor for sudden infant death syndrome[12]. One case control study of smoking and its relation to sudden infant death syndrome performed in the Scandinavian countries confirmed that tobacco smoking is an independent risk factor for SIDS and is predominately mediated through maternal smoking during pregnancy (crude odds ratio 4.0). The study also verified a strong dose-response association, and that smoking cessation or smoking less may benefit in reducing the risk.

There are over 70 case-control or cohort studies demonstrating that maternal smoking in pregnancy is associated with SIDS (pooled OR 3.9)[21].

Postnatal exposure of the infant to tobacco smoke has emerged as an additional independent risk factor for sudden infant death syndrome[22]. Mitchell el al performed a nationwide case-control study comparing 485 SIDS deaths with 1800 control infants, investigating the effect of passive tobacco smoke exposure. They found that infants of mothers who smoked after birth had an increased risk of SIDS, compared to infants of nonsmokers. They also found that smoking by the father or other household members increased the risk, odds ratio 2.41 and 1.54 respectively[23].

The independent effect of postnatal exposure is difficult to assess, because parental smoking behaviors during and after pregnancy are correlated. Mitchell et al attempted this in a review, pooling studies that reported on paternal smoking when the mother was a non-smoker, finding the pooled RR to be 1.49[22].

5.3.1 Pathophysiological mechanisms of smoking and SIDS

Prenatal exposure to tobacco has been shown to affect fetal growth and is associated with increased risk of preterm birth and low birth weight; both of which are risk factors of SIDS[24]. Greenough et al performed a study showing that prenatal exposure to tobacco smoke results in impairment of lung growth, particularly affecting airway conductance, which is likely to contribute to vulnerability for the adverse consequences of viral respiratory infections[25], which in turn are more common in infants of smoking parents[26].

Numerous studies have examined maternal smoking and its association with SIDS. It has been suggested that maternal smoking may alter autonomic control[24,27,28], thus increasing infant vulnerability to SIDS. Infants exposed to maternal smoking have been shown to exhibit altered heart rate and blood pressure control during stress when compared with control infants.[27,28] Studies, using different stimuli, have shown functional impairment of both arousal[29] and of the respiratory response to hypoxia in infants exposed to tobacco smoke in utero [30]. Arousal responses to hypoxia are believed to be of vital importance and a failure to arouse has been postulated as a potentially important component of the pathophysiology leading to sudden infant death syndrome[31].

5.4 Bed-sharing

Several studies have shown an increased risk for sudden infant death syndrome associated with bed sharing after introduction of successful public health recommendations to place infants in the prone sleeping position. Stray-Pedersen et al demonstrated that the incident of SIDS among infants below two months of age had not changed by the Back to Sleep campaign in Norway, and that 73 % of these SIDS victims were found dead sharing their bed[32].

Vennemann et al conducted a meta-analysis to investigate the association between bed sharing and sudden infant death syndrome risk. They reported that sharing strongly increased the risk of SIDS, combined odds ratio when compared to non-bed sharing infants was 2.89. The risk was highest for infants of smoking mothers and infants younger than 3 months old[33].

Similar to the findings above have also been reported in a new large meta-analysis, where five large SIDS case-control studies were combined, including 1472 SIDS cases and 4679 controls from Europe and Australia. The study demonstrated that bed sharing significantly increased the SIDS risk for breastfed infants younger than 3 months, when neither parent smoked or other risk factor where present, the adjusted odds ratio for bed sharing compared to room sharing was 5.1. Parental smoking, maternal alcohol consumption and/or drug use were shown to greatly increase the risk associated with bed sharing. The study predicted that 81 % of SIDS death among breastfed babies < 3 months with no other risk factor could have been prevented if they had not slept in the same bed as their parents[34].

Other factors that have been emphasized to greatly increase the risk with bed sharing include soft sleeping surfaces such as waterbeds, sofas and armchairs, additional bedding such as pillows and blankets and multiple bed shares[35].

5.4.1 Pathophysiological mechanisms of bed-sharing and SIDS

The mechanism by which bed sharing increases the risk of SIDS is unknown[36]. Previously, bed sharing has become associated with “overlaying”. It has been suggested that parental sedation, fatigue and obesity can cause infantile asphyxia by accident[9]. Other postulated mechanisms include airway obstruction, thermal stress, head covering and hypoxia due to rebreathing of expired gases. Bed sharing has been shown to promote infant arousal, a finding that suggests that arousal defects may not contribute to SIDS[36].

Studies have found that bed sharing infants have more bedding[33], and a higher skin[33] and rectal temperature[9] than infants sleeping alone, defending the thermal stress hypothesis. It has been suggested that sleeping next to a warm adult body and being covered by a heavy, warm adult blanket could result in an elevation of the infant's body temperature[9]. Epidemiological studies have reported that bed sharing particularly increases the SIDS risk for infants younger than 3 months old, suggesting that young infants are unable to free themselves from dangerous situations or find it difficult to wake up and alarm their parents when they are too hot or covered accidentally by blankets[33]. Furthermore, cribs are beds that are specially designed to meet safety standards for infants; adult beds are not and can therefore carry a risk of accidental entrapment and suffocation[37].

It has been argued that it may be the way we bed share rather than bed sharing itself that is decisive, because of the increased risk of bed sharing by parental smoking, alcohol and/or drug use[34].

5.5 Soft bedding and overheating

There is some evidence that the risk of SIDS is associated with the amount of clothing and blankets on an infant and the room temperature[20,38,39]. Ponsonby et al demonstrated in a case-control study of 58 SIDS infants and 120 controls that the increased risk of overheating was particularly evident when infants were sleeping in a prone position and heat loss from the face was reduced[20,19]. A previous study performed by the same researchers, found infants who had died of SIDS to be significantly overdressed for a given room temperature compared with control infants[38].

Fleming et al reported that infants dying of sudden infant death syndrome were more likely to be sleeping prone, to have been more heavily wrapped, and to have had heating on all night, when compared with the controls and concluded that overheating and the prone position were independently associated with an increased risk of SIDS[39].

It remains however unclear whether the relationship to overheating is an independent factor or simply a reflection of the increased risk of SIDS and suffocation with blankets and other objects in the sleep environment. Head covering during sleep has been reported to be of particular concern[35].

Blair et al reported in a systematic review of population-based age-matched controlled studies that the pooled prevalence of head covering in SIDS victims was 24.6 % compared to 3.2 % among controls. The increase in risk was significant across all studies and the estimated population attributed risk was 27.1%, indicating that avoidance of head covering could reduce SIDS deaths by a quarter[40].

Mitchell et al assessed two case-control studies: The New Zealand Cot death Study with 393 SIDS cases and a German SIDS case-control study with 333 SIDS cases. Noting that infants who died of the syndrome and were found with their head covered were often very sweaty and were also associated with a greater incidence and severity of thymic petechia, suggesting this may have been casually related to the death[41].

5.5.1 Pathophysiological mechanisms of soft bedding and overheating and SIDS

The mechanism for the increase in SIDS risk associated with the amount of clothing and blankets on an infant and the room temperature is not known[35]. Suggested causal mechanisms include mechanical occlusion of the airways, rebreathing of expired air and thermal stress[40].

Room temperature and the clothing and bedding are only two of several factors which will contribute to the thermal state of an infant. To maintain thermal balance over time, heat loss must match metabolic heat production[42]. The prone sleeping position will reduce heat loss by reducing the body surface area available for heat loss. In the heavily dressed infant, the head has an important thermoregulatory role which will be compromised by placing the head down or underneath bedding[42]. Soft bedding will further increase the area of contact[43]. Tuffnell et al estimated that thermal loss in prone infants was 60 % less than for supine sleeping infants, with the same insulation values for clothing and bedding[19]. The effect of overwrapping would be likely to be greater at the time of an infection, which increases the infant's basic metabolic rate and increases heat generation[39]. Studies have noted that parents may respond to infections in their babies by increasing the amount of clothing and bedding or warming the infant[42].

Franco et al reported that supine sleeping infants with their head covered had a decreased arousal and a higher rectal and procephalic temperature[44,45]. These observations in both studies provide support for the thermal stress hypothesis.

Mitchell et al noted an association between head covering and a greater incidence and severity of petechial hemorrhages in the thymus. The pathogenesis of petechial hemorrhages in SIDS is uncertain and it has been difficult to draw further conclusions from these results[41].

5.6 Pacifier use as a protective factor

The use of a pacifier during sleep has appeared to reduce the risk of SIDS. The hypothesis that pacifier use might protect against sudden infant death syndrome was first postulated by Cozzi et al in 1979 and support for this hypothesis was reported in 1993[46].

Mitchell et al conducted a meta-analysis to investigate the association between pacifier use and SIDS and reported that the use of a pacifier significantly decreased the risk of SIDS by 50 %. The included studies came from New Zealand, the Netherlands, United Kingdom, Republic of Ireland, Germany, Scandinavia and other European countries, and the United States and occurred both before and after the reduction in SIDS that followed the recommendation to place infants supine for sleep. The results from the different studies were consistent, showing that the use of pacifiers was associated with an approximate halving of the risk of SIDS, and came from many countries in the world, suggesting that the results are generalizable to other countries[46].

Similar to the findings above have also been reported in another meta-analysis, where seven SIDS case-control studies were combined. The study demonstrated an even lower risk of SIDS with pacifier use, particularly when the infant were placed for sleep, OR 0.39[47].

Moon et al performed a case-control study of 260 SIDS deaths and 260 matched control, to examine the association between pacifier use during sleep and SIDS in relation to other risk factors and to determine if pacifier use modifies the impact of these risk factors. The study demonstrated that pacifier use during last sleep decreased the risk for SIDS. The use decreased SIDS risk even more when mothers were ≥20 years of age, married, nonsmokers, had adequate prenatal care, and if the infant was ever breastfed. The risk was also decreased more when the infant was sleeping in the prone/side position, bed sharing, and when soft bedding was present. The association between adverse environmental factors and SIDS risk was modified favorably by pacifier use, but the interactions between pacifier use and these factors were not significant. The researches concluded that pacifier use may provide an

additional strategy to reduce the risk of SIDS for infants at high risk or in adverse sleep environments[35].

5.6.1 Mechanisms of pacifier protection against SIDS

Several mechanisms have been postulated to explain why the use of a pacifier reduces the risk of SIDS, but none has been widely accepted. Special attention has been given to pathophysiological mechanisms concerning arousal, mouth breathing/airway patency, and sleep position[47].

Franco et al have demonstrated increased arousal responsiveness in infants who frequently used a pacifier, including during sleep[48]. This finding is significant because decreased arousal to life-threatening challenges has been implicated in SIDS. The effect that pacifier use has on lowering the arousal threshold could benefit an infant who otherwise might respond inappropriately to a threatening challenge[47].

It has been hypothesized that if the nasal airway becomes blocked, the use of a pacifier improves the infant´s ability to breath through the mouth. Retroposition of the tongue has been suggested to cause obstructive apnea and asphyxiation. This position could be avoided by sucking on a pacifier, which requires positioning of the tongue forward[47]. Pacifier use has also been postulated to decrease the prevalence of prone sleeping[48].

Pacifier use has been associated with a higher risk of infective symptoms[46]. The use is associated with a 1.2-to 2-fold increased risk of otitis media, but since ear infections are less common among infants aged <6 months, the risk of developing an infection in the SIDS incidence peak is expected to be low[47].

6 Pathogenesis

6.1 General

The cause of sudden infant death syndrome is unknown [49], but it is generally accepted that SIDS probably marks the end of a series of risk factors and pathophysiological responses. It is believed that the SIDS victims consist of several subgroups, each with its own distinctive characteristics and predispositions[1]. More than 400 different hypothesis and theories have supposedly been proposed[50].

6.2 Pathological features

There are no autopsy findings pathognomonic of SIDS and no findings for its diagnosis. There are, however, several common observations. Petechial hemorrhages of the thymus gland, visceral pleura and epicardium occur in 85 to 95% of SIDS death. It has been presumed, but by no mean proved, that intrathoracic petechiae in SIDS result from upper airway obstruction or terminal gasping[1], but the site of the assumed obstruction has never been established[51] and the distribution and density of petechiae differs from what is found in asphyxia[52].

Frothy, mucoid, and pink or bloody oronasal secretions are frequently observed in SIDS cases[1]. The lungs are often found to be partly collapsed[50], congested and edematous, findings that are believed to be evidence of terminal left ventricular failure[1]. Hemosiderin in the lungs may be a sign of previous trauma or asphyxal episodes, and fresh blood in the nostrils is indicative of more recent injury[1]. Scattered foci of inflammations cells in the respiratory epithelium are another common finding in SIDS, but the degree of inflammation in the trachea and bronchioles is considered insufficient to cause death[49].

6.3 Etiology

6.3.1 Brainstem abnormality

The brainstem hypothesis postulates that a defect in brainstem-mediated protective responses to homeostatic stressors during sleep in a critical developmental period is the cause of a

majority of SIDS cases. Abnormalities in the medullary 5-HT system, involved in 70 % of SIDS cases are the most solid neurochemical findings to date.[53]. Extensive experimental analysis indicates that the serotonergic (5-hydroxytryptamine) system of the medulla oblongata is critical for the modulation and integration of a variety of homeostatic functions, such as respiratory drive, blood pressure regulation, thermoregulation, upper airway reflexes and arousal[54].

Paterson et al examined frozen medullae from infants dying from SIDS or from causes other than SIDS, comparing markers of 5-HT function, in effort to investigate the pathogenesis of the 5-HT abnormalities in greater detail. Compared to controls, SIDS cases had a higher quantity and density of 5-HT neurons and a lower density of 5-HT1A receptor binding sites in regions of the medulla involved in homeostatic function. The ratio of 5-HTT binding density to 5-HT neuron count in the medulla was significantly lower in SIDS cases compared with controls. The present report demonstrates that the deficiencies in the medullary 5-HT system are quite extensive, potentially including abnormal 5-HT neuron firing, synthesis, release and clearance. The study also found a reduced 5-HT1A receptor binding density in male compared with female SIDS cases, suggesting why males are more vulnerable to SIDS[54].

Studies have examined the relationships between epidemiological risk factors for SIDS and changes in serotonergic expression, demonstrating associations with exposure to cigarette smoke, prone sleep position and bed sharing. Machaalani et al reported that exposure to nicotine was significantly associated with 5HT1A changes in several medullary nuclei, providing a potential etiological mechanism between parental smoking and SIDS risk[55].

6.3.2 Long QT-interval

The control of cardiac function has been proposed to be suboptimal in infants at risk of SIDS, but results from studies have been inconsistent. The hypothesis that some cases of SIDS could be caused by a lethal cardiac arrhythmia precipitated by a QT interval prolongation was suggested in 1976[56]. Schwartz et al conducted a large prospective study to test this hypothesis. Electrocardiograms were recorded on the third or fourth day of life in 34,442 newborns that were then followed for one year. Among the 34 deaths in this cohort, 24 were due to SIDS. The infants who died of SIDS had a longer corrected QT interval (QTc) compared to the survivors and those who died from other causes. The QTc was > 440 msec in 12 of the 24

SIDS infants. The study verified a strong association between prolonged QTc and SIDS, with 41.3 in odds ratio[57].

Long QT syndrome is a disorder characterized by QT interval prolongation on the ECG and tendency to life threatening arrhythmias. The syndrome is caused by genetic mutations in several genes encoding cardiac ion channels. All features of LQTS are consistent with the definition of SIDS, including a negative postmortem examination[58].

Given the limitations of small sample sizes in studies of rare conditions, the incidence and role of cardiac abnormalities in SIDS remains a subject of debate. Based on a Norwegian cohort study of the prevalence of genetic variants associated with LQTS, such abnormalities appear to be present in less than 10 % of SIDS victims[58].

6.3.3 Inflammation and infection

Several aspects make an infectious etiology for SIDS attractive. Mild infections are commonly seen in up to 50 % of SIDS cases in the days prior to death[50]. The incidence of SIDS has been reported to be highest in the winter months, which accompany the increased incidence of several infections during this season, predominantly those of the respiratory tract[1]. Inflammatory changes in the respiratory epithelium on postmortem examination are a common finding in SIDS**,** but the degree of inflammation in the trachea and bronchioles is considered insufficient to cause death. Infants who have succumbed to SIDS have been found to have an increased amount of immunoglobulin producing cells in their salivary glands and tracheal wall. These immunoglobulin producing cells proposes a recent stimulation of the mucosal immune system[49]. SIDS also accompanies a period of rapid development of the immune system[59].

Hypoxanthine concentrations in vitreous humor have been determined in cases of sudden infant death syndrome and compared with levels in cases of infectious death and violent death[60]. Hypoxanthine is a biochemical indicator of hypoxia that accumulates in body fluids during hypoxic degradation of ATP within minutes after a hypoxic incident[61]. The hypoxanthine levels were significantly ($p < 0.01$) higher in SIDS than in violent deaths, while no significant difference was found between SIDS and infectious deaths. The present report demonstrates a similar distribution pattern of hypoxanthine levels in vitreous humor in SIDS

and infectious death, indicating that the death mechanism in SIDS has some similarities with infectious death[60].

Cerebrospinal fluid from infants who died of SIDS has been examined with respect to concentrations of interleukin-6. The examination reveled that half of the SIDS infants had elevated levels of IL-6. The IL-6 concentrations in their cerebrospinal fluid were equivalent to those found in infants dying from infectious diseases like meningitis and septicemia. IL-6 has an important function in immune responses and can induce fever, demonstrating that immune activation may play a significant role in SIDS. The presence of cytokines in the central nervous system can cause respiratory depression[62].

Vege et al conducted a study to investigate whether there is a relationship between central immune response in SIDS, indicated by increased CSF IL-6 levels, and peripheral immune stimulation as expressed by the presence of IgA, IgG, and IgM immunocytes and T lymphocytes in the laryngeal mucosa and HLA-DR expression in the surface epithelium and in the glands of the laryngeal wall. The study shows that the laryngeal mucosa in SIDS victims with high IL-6 levels in the cerebrospinal fluid also show signs of immune stimulation with increased numbers of IgA immunocytes and increased expression of HLA-DR in the epithelium. Many of these infants showed signs of infection prior to death and were found dead in a prone position. Because the IL-6 concentrations in their CSF corresponded to the levels found in infants who died from infectious diseases such as meningitis, septicemia and pneumonia, the findings indicate that SIDS may be caused by an "overreaction" of the immune system to a generally harmless infection[63].

The hazard of sleeping prone has been attributed to increased risk of infection. The prone position has been shown to raise the upper airway surface temperature to levels that is required for induction of pyrogenic toxins from the potentially pathogenic bacteria Staphyloccocus aureus[64]. Both viruses and bacteria are thought to play a role in SIDS[59], but S. aures has been suggested to be the prime candidate[65]. The bacterium is common in the early months of life when SIDS reaches a peak and it´s toxins have been identified in approximately 53 % of SIDS victims[65].

Horne et al performed a study comparing arousal from sleep in infants on the day they were released from the hospital after an infection with those when fully recovered and with a set of

control infants. The results show that arousal from quiet sleep is defective following an infection and could explain the increased risk for SIDS[66].

6.3.4 Hypoxemia

The hypothesis that recurrent or prolonged hypoxemia may be an important pathophysiological mechanism underlying SIDS has acquired a great deal of attention the past decades. Sustained or intermittent hypoxia promotes the formation of vascular endothelial growth factor, an endothelial cell-specific mitogen that stimulates to angiogenesis, which increases peripheral oxygen delivery. Even small changes in tissue oxygenation can result in considerable adjustments in VEGF expression. Jones et al demonstrated that concentrations of VEGF in cerebrospinal fluid was significantly higher in 51 infants who died of SIDS than 31 control infants who died of an identifiable cause, indicating that hypoxia frequently precedes death from SIDS[67].

6.3.5 Other hypothesis

Several researches claim that sudden infant death syndrome can be triggered by reflex mechanisms; vagal reflexes can induce apne and cardiac arrhythmias. Other researchers have shown an interest in the possible role of mitochondrial DNA mutations in sudden infant death, which may induce ATP-depletion. These mutations have been detected in some SIDS cases and it has been suggested that a reduced ATP-production can be fatal in association with increased stress due to a prone sleeping position with the head facing down in loose bedding, in a combination with warm surroundings and an upper respiratory infection[50].

6.4 The Fatal triangle hypothesis

The pathogenesis of SIDS is still incompletely defined, but efforts have been made trying to summarize the complex interaction between intrinsic and extrinsic factors in a fatal triangle hypothesis. This hypothesis proposes that SIDS can occur if three conditions are fulfilled:

1, a vulnerable infant with an underlying susceptibility;
2, an exogenous stressor at the time of death; and
3, the critical developmental period, with a peak at 2 to 4 months.

The infant´s vulnerability lies latent until he/she enters a crucial period and is subject to an exogenous stressor. This concept provides help in order to relate current epidemiological and biochemical research[50,68].

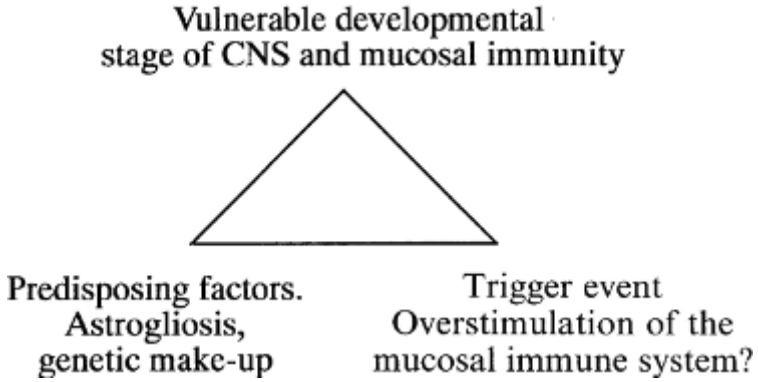

Fig. 2. The fatal triangle
From Rognum et al. 1993[74]

7 Classification and diagnostic criteria

7.1 Diagnostic challenges – what is unexplained and what is explained

What we recognize today as sudden infant death syndrome can be presented in a pie chart, Fig 3. Explained deaths represent about 40 % of the circle, including diagnoses such as long QT-syndrome, fatty oxidation defects and other yet to be discovered [59]. The remaining percentage might be "genuine SIDS" which could possibly be explained by the fatal triangle. Identified modifiable risk factors for SIDS may have additive effects and act in concert to start the vicious circle of SIDS. For instance an infant in a vulnerable age period with a mild infection combined with prone position, warm environments and possibly certain genetic factors could experience a sequence of inflammatory and physiological responses which in turn trigger the vicious circle of events leading to hypoxemia, hyperthermia and stimulation of the immune system, ending with hypoxia, coma and death, fig 4[59].

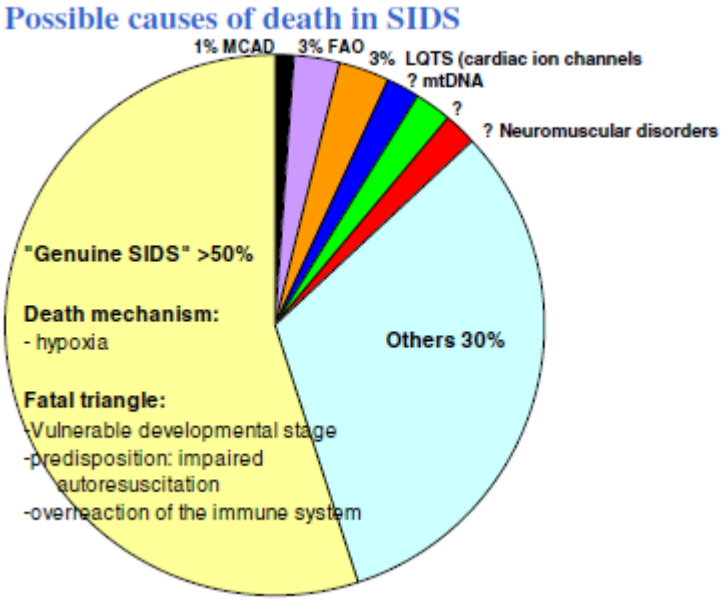

Fig. 3 Possible causes of SIDS.
From Vege et al. 2004[59]

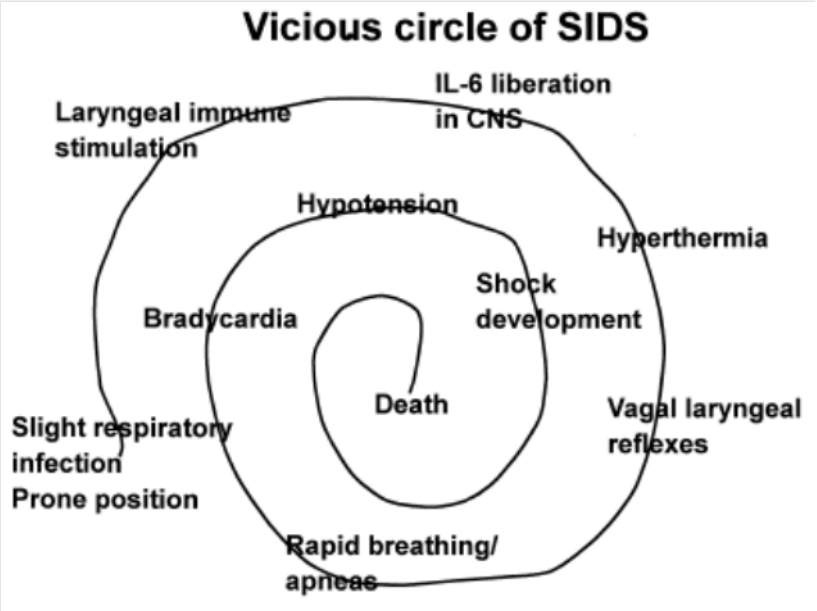

Fig. 4. "The vicious circle of SIDS".
From Vege et al 1999[63]

Various autopsy approaches, different applications of diagnostic criteria and inconsistent use of definitions have resulted in contradictions and lack of consistencies in the literature[69] and a false impression of SIDS rates around the world[59]. The "grey zone" of diagnoses has become more prominent since the decrease in SIDS rate in most countries after the Back to Sleep campaigns. The genuine SIDS cases have decreased, while the relative proportion of explained deaths has increased[70]. This development has led to an increase in proportion of deaths due to neglect, abuse and homicide, cases which are often difficult to diagnose[59] because of subtle evidence and difficulties distinguishing them from SIDS[71].

Researchers have tried to develop standards for diagnostic protocols explaining in detail the investigation that should be conducted to ensure optimal investigation of individual cases and to facilitate international comparisons of statistics. Baseline forensic autopsy includes radiological, toxicological and microbiological tests, neuropathological examination, and histology of all organs and targeted genetic screening[69,71].

7.2 Routines in Norway

Health services in Norway encounter sudden infant death syndrome more seldom today because of the reduced incidence after the introduction of the back-to-sleep campaign. It has

resulted in a lack of experience among health workers and increased risk for inadequate routines[50].

Every case of sudden and unexpected infant deaths is admitted to nearest children´s ward where a conventional hospital chart is carried out in the hospital's management. These deaths are always regarded as unnatural; and the physician has a duty to immediately notify the police. The police are required to initiate investigations of all cases of children dying suddenly and unexpectedly[72]. If the autopsy and the circumstances surrounding the death do not suggest unnatural death, the police will end their engagement and further follow-up is done by the health system. Landsforeningen Uventet Barnedød (LUB) provides information and support to both health professionals and the affected families[73].

The health care system is required by law to provide a death scene investigation in all cases of children less than 4 years of age who dies suddenly and unexpectedly. This requirement was first introduced in November 2010. It is the hospital where the child was admitted that has the responsibility to inform parents or caregivers both in speaking and writing on the offer of voluntary death scene investigation[72].

The death scene investigation is carried out by a team of two people under the leadership of the National Public Health Institute and by the Forensic Institute in Oslo[73]. It is important to compare the results of the autopsy with the results from the location of death; therefore it is desirable that the doctor who conducted the autopsy also participates in the examination of the death scene (or another person with forensic expertise). The second team member is one who has knowledge and experience of death scene investigations. The purpose of this voluntary investigation report is to clarify what caused the child's death. This is necessary to provide proper diagnosis and to get information that may help to prevent similar cases. Parents or guardians must give written consent to a death scene investigation[72].

Parents and caregivers have the opportunity to ask questions to the team that comes to the place of death. It has been demonstrated that there are many parents who make use of and appreciated this opportunity. Although the purpose of a death scene investigation is not to provide health care to the parents, many parents have experienced the investigation as useful and important[72].

All available information is thoroughly discussed in a multidisciplinary meeting when the investigation report has been completed. The findings are compared and the final conclusion

about the cause of death is drawn. This information is also provided in a follow-up conversation with the parents[72].

8 Recommendations for a safe infant sleeping environment

1. All infants should be placed to sleep on their backs for every sleep by every caregiver. Side sleeping is not safe and is not advised.

2. Infants should always be placed to sleep on a firm sleep surface, covered by a fitted sheet, to reduce the risk of SIDS and suffocation.

3. Infants should sleep in a crib placed in the parents' bedroom close to the parents' bed.

4. Keep soft objects and loose bedding out of the crib to reduce the risk of SIDS, the infants head should remain uncovered.

6. Maternal smoking during pregnancy and smoke in the infant's environment after birth should be avoided.

7. Prenatal and postnatal exposure to alcohol or illicit drug use should be avoided.

8. Breastfeeding is recommended.

9. Consider offering a pacifier at nap time and bedtime. Pacifier should be introduced after breastfeeding has been well established.

10. Avoid overheating; infants should be dressed appropriately for the sleeping environment[73]

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